

Systematic review of the evidence for rational dosing of colistin

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Background. There is an alarming global increase in the incidence of nosocomial infections with multidrug-resistant Gram-negative bacteria, which are often only susceptible to colistin. Colistin was developed prior to current methods of establishing dosing using pharmacokinetic-pharmacodynamic relationships. Dosing regimens differ in package inserts from different manufacturers and in different guidelines. It is imperative to avoid under-dosing with colistin in order to limit the development of resistance, as it is the last line of defence.

Methods. We conducted a systematic review of the literature to develop guidelines for rational dosing of intravenous colistin, with a particular focus on critically ill patients.

Results. Colistin is administered as the inactive pro-drug colistimethate sodium. Colistin demonstrates concentration-dependent bacterial killing, suggesting that higher doses should be administered less frequently to achieve higher peak concentrations. Dose-related nephrotoxicity occurs, making it impossible to safely achieve concentrations that prevent the selection of resistant mutants or the effective eradication of bacteria with higher minimum inhibitory concentrations. Theoretically, combination therapy should be used to reduce the risk of selection of resistant bacteria. In critically ill patients, a loading dose should be given to rapidly achieve therapeutic concentrations, followed by maintenance doses of 4.5 MU 12-hourly. Maintenance dose adjustment is necessary with renal impairment.

Conclusion. Easier access to colistin is needed in South Africa, where it is not a registered medicine. Further research is needed to better characterise colistin's pharmacokinetic-pharmacodynamic relationships in humans and to establish whether combinations of colistin with other antimicrobials result in improved clinical outcomes or a reduction in selection of resistant bacteria.

S Afr Med J 2014;104(3):183-186. DOI:10.7196/SAMJ.7011



Since the discovery of antimicrobial agents, ever-evolving mechanisms of microbial resistance have been shaping the field of infectious diseases. Globally multidrug-resistant (MDR) Gram-negative bacilli causing nosocomial infections (notably in *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterobacter* sp. and *Acinetobacter baumannii*) have become an important emerging threat.^[1]

In South Africa (SA), carbapenem resistance is emerging in *K. pneumoniae* and *Enterobacter* sp. while high levels of resistance to all antimicrobial classes are observed among *P. aeruginosa* and *A. baumannii*.^[2] *A. baumannii* is a common pathogen in intensive care units (ICUs).^[3] The antimicrobial susceptibility patterns of isolates of bacteraemic *A. baumannii* complex isolates over time in the public and private sectors in SA are shown in Figs 1A and 1B, respectively. Particularly striking is the decline in carbapenem susceptibility from 35% in 2007 to only 17% in 2011 in the public sector. More than half the isolates in the private sector were resistant to carbapenems, but there was no clear downward trend. Inappropriate antibiotic prescription practices in ICUs in the public and private sectors in SA are common and associated with poor patient outcomes.^[4] Both carbapenem resistance and inappropriate antibiotic use are associated with increased mortality in patients with *Acinetobacter* bacteraemia.^[5-8]

Many acinetobacteria and other MDR Gram-negative bacteria are only susceptible to colistin (polymyxin E). Colistin is not a registered medicine in SA, but it can be obtained via a Medicines and Related Substance Act, Section 21 application to the Medicines Control Council. The polymyxin group of antibiotics was discovered in the 1940s,^[9,10] but their popularity soon faded due to reports of

nephrotoxicity and the availability of safer antibiotics in the 1970s.^[11] Important pharmacokinetic and pharmacodynamic data for colistin are lacking, which are necessary for safe and effective dosing, particularly in critically ill patients and those with impaired renal function.^[12] No international consensus exists on the correct dose, and dosing units are not standardised. Package insert dosing instructions differ between manufacturers. An additional problem is that prescribing units differ between manufacturers, including mg for colistin base activity (CBA) and colistimethate sodium (CMS), and international units for CMS. This creates confusion among clinicians and complicates interpreting the available literature. The product accessed in SA (Colimycine) is labelled in international units. One million units (MU) of CMS is roughly equivalent to 80 mg of CMS and 30 mg of CBA.

Under-dosing of colistin increases the risk of the development of resistance and hetero-resistance, which is important as colistin is the last line of defence against MDR Gram-negative bacteria. Colistin resistance was first reported in the Czech Republic in 1999 and worldwide reports are accumulating at an alarming rate.^[13] Eighteen of 132 (13.6%) bloodstream isolates of *A. baumannii* complex were resistant to colistin in Groote Schuur Hospital, SA, during 2011.

Methods

We conducted a systematic review of the evidence for rational dosing of intravenous (IV) colistin, with a particular focus on patients who are critically ill or have renal impairment. English language, peer-reviewed journal publications (predating April 2013) were identified by searching the PubMed database. The search terms included various combinations of the following keywords: polymyxins;

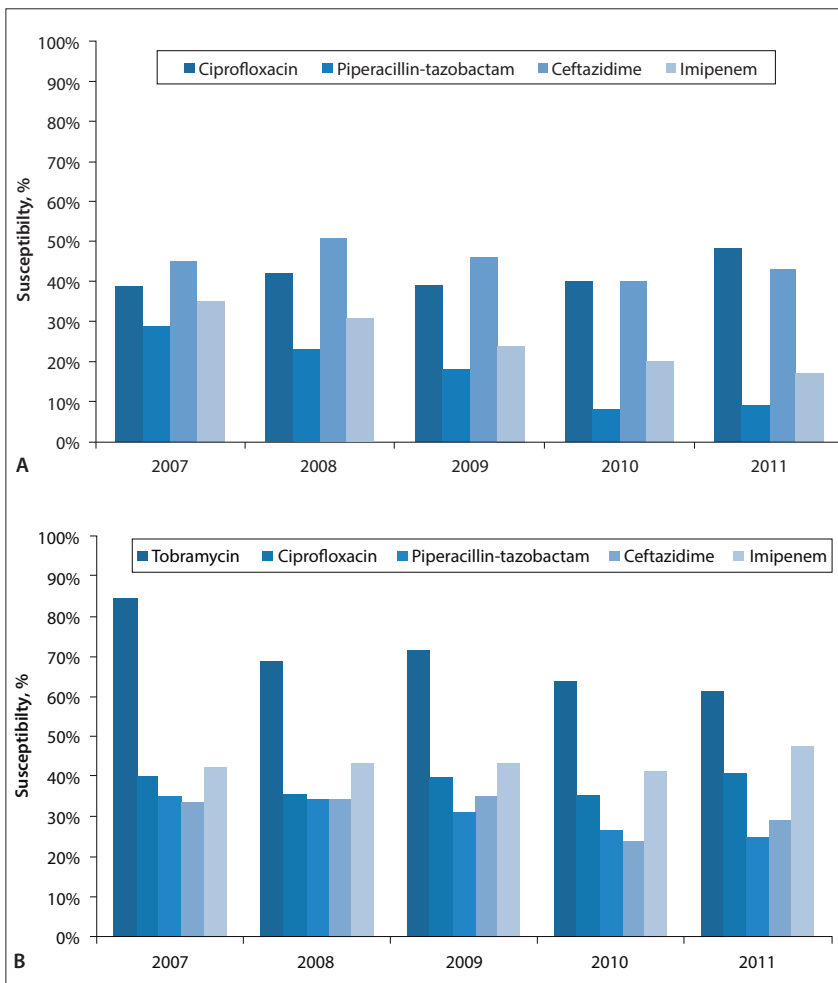


Fig. 1. Susceptibility of *A. baumannii* complex blood isolates to selected antimicrobial agents at laboratory sites in South Africa, 2007 - 2011. (A) Five large public sector (2011 susceptibility data are based on provisional results);^[2,43] and (B) eight private sector laboratory sites (personal communication, Colleen Bamford for the National Antibiotic Study Forum).

colistin; colistimethate sodium; intravenous; severe sepsis; critically ill; pharmacokinetics; pharmacodynamics; dosing; dosing units; dosing interval; nephrotoxicity; renal failure; renal replacement; resistance; combination therapy; MDR Gram-negative infections; *Acinetobacter*; *Pseudomonas*; and *Klebsiella*. After reviewing the abstracts, relevant full-text manuscripts were retrieved. Additional articles were identified by hand searching the references of articles obtained by the electronic search strategy. Finally, based on the evidence obtained, an IV colistin dosing guideline for the treatment of MDR Gram-negative infections was developed, with a particular focus on critically ill patients.

Results

Pharmacokinetic overview

Colistin is administered intravenously as the inactive pro-drug CMS, which is hydrolysed to active colistin.^[14] In critically ill patients, colistin plasma concentrations

peak seven hours after CMS administration. The half-lives of CMS and colistin are 2.3 and 14.4 hours, respectively.^[15] Distribution to cerebrospinal, pleural and synovial fluid is poor.^[10] Unconverted CMS is predominantly eliminated by the kidneys, partly by tubular secretion. By contrast, colistin is predominantly cleared by unknown non-renal mechanisms and undergoes extensive renal tubular reabsorption.^[16]

Dose adjustment in renal failure

In patients with renal impairment the elimination of CMS is decreased and a greater fraction of the administered dose is converted to colistin,^[17-19] necessitating a dose adjustment. Both CMS and colistin are efficiently cleared by venovenous haemofiltration^[20] and haemodialysis.^[17,21-22] Therefore, a supplemental dose of colistin needs to be given after dialysis and higher doses are required in patients undergoing venovenous haemofiltration.

Loading doses

Drugs take 4 - 5 times their half-lives to reach target steady-state plasma concentrations. A loading dose is required in serious infections to rapidly achieve therapeutic concentrations. Critically ill patients with severe sepsis have significant capillary leak,^[23-24] which increases the volume of distribution of colistin 4 - 15-fold.^[25-26] The loading dose in critically ill patients is therefore higher than in less-ill patients.^[15,17] It is important to note that the magnitude of the loading dose is not affected by renal impairment; only subsequent maintenance doses or dose intervals should be adjusted.

Pharmacokinetic-pharmacodynamic relationships

Colistin has no activity against Gram-positive bacteria and anaerobes,^[10] but rapidly kills Gram-negative bacteria in a concentration-dependent manner.^[14,19,27] The bactericidal activity of colistin is partly due to its detergent effect on the bacterial cell membrane.^[10,19,28] This disruptive effect on membrane integrity may account for the *in vitro* synergy observed with certain antimicrobials (e.g. rifampicin).^[28] Murine studies showed that the most predictive index for antibacterial effect against *P. aeruginosa* and *A. baumannii* was the ratio of the area under the curve to the minimum inhibitory concentration (AUC/MIC).^[29-30]

Extrapolating from murine AUC/MIC colistin data, Garonzik *et al.*^[17] estimated that in humans a total colistin AUC/MIC of 60 is the average achieved using currently recommended doses. This AUC/MIC of 60 would be expected to result in a suboptimal pharmacodynamic effect of somewhere between stasis and 1 log₁₀ kill for most susceptible bacteria. The authors acknowledge that there are limitations to their estimates as free concentrations of colistin were measured in the murine infection models^[29-30] and there are no human data on the protein binding of colistin. Peak concentrations of at least 4 mg/l (four times the MIC) were needed to eliminate *P. aeruginosa* in one study, but in critically ill patients this concentration was only reached with doses of 9 MU of CMS.^[31] A recent *in vitro* study showed that the mutant prevention concentration (at which 90% of isolates tested were prevented from developing mutant strains) exceeds 128 mg/l,^[32] a concentration not achievable with currently used doses. A high proportion of clinician-selected dosing regimens result in sub-therapeutic colistin concentrations.^[12,15,17,26,31,33] Of particular concern is a recent study showing that it is not possible to reach the modest target

Table 1. IV CMS dosing guideline for the treatment of MDR Gram-negative infections

Dose	Patient category	Dosing suggestion
Loading	Critically ill or severe sepsis	9 - 12 MU*
Maintenance	eGFR >60 ml/min	4.5 MU 12-hourly
	eGFR 30 - 60 ml/min	3 MU 12-hourly
	eGFR 10 - 30 ml/min	2 MU 12-hourly
	eGFR <10 ml/min	1 MU 12-hourly
	Intermittent haemodialysis	1 MU 12-hourly plus supplemental dose of 1 MU after each episode of dialysis
	Continuous renal replacement	4.5 MU 12-hourly†

IV = intravenous; CMS = colistimethate sodium; MDR = multidrug-resistant; eGFR = estimated glomerular filtration rate.
 *Loading dose is calculated according to ideal body weight: 12 MU CMS for 70 kg and 9 MU for 55 kg patients.
 †Garonzik *et al.*^[17] recommend higher daily doses of 16 MU as both CMS and colistin are filtered during renal replacement therapy.

colistin AUC/MIC of 60 in patients with creatinine clearances >70 ml/min without exceeding the upper limit daily dose of 10 MU CMS recommended in the package insert.^[17]

Dosing interval

The recommended dosing intervals of colistin range between 6 and 12 hours. The long half-life of colistin suggests that less frequent dosing intervals should be adequate. On theoretical grounds giving higher doses less frequently should result in higher peak concentrations and more effective bacterial eradication. However, extended dosing intervals may lead to periods of low colistin concentrations allowing for resistant subpopulations to occur within a microbial population susceptible to colistin (hetero-resistance).^[28-30,34] Small, uncontrolled studies report good efficacy, without significant renal toxicity, of high-dose CMS regimens given 12-hourly^[35] or daily.^[31] There are no randomised, controlled, clinical trials (RCTs) evaluating the efficacy and safety of once-, twice- and thrice-daily dosing of colistin.

Combination therapy

A strong theoretical basis exists for the use of colistin as part of combination antimicrobial therapy to maximise antimicrobial activity and to reduce the risk of the emergence of resistance, especially in patients with normal renal function or with bacterial MICs >1 mg/l.^[10,17] As discussed above, currently used doses (9 MU CMS per day in divided doses) can neither achieve the modest target AUC/MIC of 60 in patients with normal renal function,^[17] nor prevent the selection of resistant mutant subpopulations.^[10,32]

Many studies have proposed different colistin combination regimens. The most frequently studied are combinations of colistin with rifampicin or the carbapenems,^[13] which both showed synergy *in vitro*.^[36] Other *in vitro* studies report effective combinations with tigecycline, amikacin, fosfomycin, azithromycin, ceftazidime, minocycline and, surprisingly, the glycopeptides vancomycin and teicoplanin.^[10,13] Combination with levofloxacin or tobramycin decreased the mutant selection window of colistin.^[37] Some *in vitro* antibiotic combination studies demonstrated bactericidal activity even against colistin-resistant strains and others showed bactericidal activity at sub-MIC concentrations of colistin.^[28] There is an urgent need for RCTs comparing the efficacy of different combinations of antimicrobial agents with colistin. One trial showed that the 30-day mortality rate of patients with serious MDR *A. baumannii* infections was not reduced by the addition of rifampicin to colistin, but the study was limited by the relatively low total daily dose of CMS (6 MU) used.^[44]

Nephrotoxicity

In contrast to initial reports that colistin's nephrotoxicity rates approached 50%, the majority of recent studies report much lower renal toxicity rates of 10 - 30%.^[38] A local study found that the risk of nephrotoxicity of colistin (dosed at the relatively low total daily dose of 6 MU of CMS) was similar to that of tobramycin.^[39] Colistin's nephrotoxicity is dose-dependent and mostly mild and reversible.^[25,38,40] One study showed that rates of nephrotoxicity were significantly higher in patients receiving daily maintenance doses greater than the equivalent of 12 MU of CMS in a 70 kg patient.^[38] Colistin's exact mechanism of nephrotoxicity is not established.^[11,12,40,41] Patients with abnormal renal function at the start of colistin therapy have consistently been identified as being at high risk for nephrotoxic events.^[28] General measures to limit colistin's nephrotoxicity include regular monitoring of renal function with appropriate dose adjustment (especially with prolonged use), adequate hydration and limited use of concomitant nephrotoxic drugs. Therapeutic monitoring of CMS/colistin concentrations is not commercially available.

Discussion

It is imperative that colistin is dosed appropriately to minimise the risk of resistance as it is a last-line agent against MDR Gram-negative bacteria, and the pipeline of new drugs in development for these organisms is very small.^[42] There are good theoretical grounds to suggest that colistin should be used in combination with other effective antibacterials, especially in patients with normal renal function and when treating bacteria with MICs >1 mg/l.^[10,17]

We used the information gleaned from our systematic review to develop simple recommendations for rational dosing (Table 1). A key study that informed our recommendations was conducted by Garonzik *et al.*,^[17] who integrated population pharmacokinetic data with pharmacodynamic data in a model to estimate dosing in critically ill patients with a wide range of renal function (including those receiving renal replacement therapy). Even though the maintenance doses we recommend are higher than in the package insert of the currently used unregistered product in SA, these will still only result in concentrations that have suboptimal bacterial killing. Higher doses are likely to result in unacceptable rates of nephrotoxicity.^[38] We suggest 12-hour dosing intervals in view of the long half-life of colistin (14 hours) and because of the theoretical benefit of the resulting higher peak concentrations, but, as discussed above, 8-hourly dosing is also acceptable. CMS is unstable in aqueous solutions, therefore it should be administered shortly after reconstitution.^[10] All critically ill patients with severe sepsis, regardless of their renal function, require a loading dose of 9 - 12 MU of CMS to ensure the rapid attainment of

therapeutic concentrations.^[15,17] The loading dose range in the table is based on ideal body weight. The loading dose should be administered intravenously over 1 - 2 hours, followed by the first maintenance dose after 12 hours.^[15] Maintenance doses can be given as IV infusions over 15 min.^[26] In patients with an estimated glomerular filtration rate <60 ml/min, CMS dose adjustment is required. Twelve-hourly dosing is appropriate in patients with renal impairment, because only CMS, the inactive pro-drug, is subjected to renal elimination (not the active drug colistin). CMS doses equal to or even higher than the daily dose in patients with normal renal function are required in patients on continuous renal replacement therapy, because both CMS and colistin are removed.^[17,22] Garonzik *et al.*^[17] recommend a daily dose of 16 MU of CMS in this setting.

There is a clear need for further research on colistin, particularly to establish pharmacokinetic-pharmacodynamic relationships in humans. More RCTs need to be conducted to determine if combination therapy results in superior outcomes, and, if so, which combinations should be used. Finally, access to colistin needs to be made easier in SA, especially in the public sector where carbapenem resistance is increasing.

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Accepted 16 September 2013.